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Original Research Article

Histopathological Patterns of Splenic Involvement in Nodular Non-Hodgkin's Lymphoma: A Multicenter Cross-Sectional Study

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Abstract: ***Background:*** Splenic involvement in nodular non-Hodgkin's lymphoma (NHL) significantly influences disease staging, prognostic assessment, and therapeutic decisions. Also region-specific data from Pakistan regarding the histopathological patterns of splenic involvement remain scarce. This study aimed to determine the frequency and histopathological patterns of splenic involvement in patients with nodular NHL presenting at major tertiary care centers in Lahore, Pakistan. ***Methodology:*** This multicenter cross-sectional study was conducted at Fatima Memorial Hospital, Chughtai Lab, and Sir Ganga Ram Hospital, Lahore, from October 2023 to October 2025. A total of 87 consecutive patients with histopathologically confirmed nodular NHL were enrolled. Splenic involvement was assessed through imaging by abdominal ultrasonography followed by ultrasound-guided fine-needle aspiration cytology in cases with focal lesions. Histopathological patterns were classified according to standardized criteria: nodular, diffuse, mixed, or miliary. Immunohistochemically subtyping was performed using the WHO Classification. Data were analyzed using SPSS using latest version. ***Results & Findings***: The mean age of patients was 52.4 ± 16.7 years, with a male predominance (66.7%). Splenic involvement was identified in 28 patients (32.2%; 95% CI: 22.9–42.8). Among these, the nodular pattern was most common (46.4%), followed by diffuse (32.1%), mixed (14.3%), and miliary (7.1%) patterns. Diffuse large B-cell lymphoma (DLBCL) was the most frequent subtype (51.7%), followed by follicular lymphoma (25.3%), mantle cell lymphoma (12.6%), and marginal zone lymphoma (8.0%). Splenic involvement showed significant associations with advanced-stage disease ($p < 0.001$), presence of B-symptoms ($p = 0.008$), and bone marrow infiltration ($p = 0.02$). Pattern-wise analysis revealed that nodular involvement predominated in follicular lymphoma, whereas diffuse infiltration was more commonly observed in DLBCL. Conclusion: Splenic involvement occurs in approximately one-third of patients with nodular NHL in the urban population of Lahore, with nodular and diffuse patterns being most prevalent. The pattern of involvement correlates with lymphoma subtype and clinical stage. These findings underscore the necessity of systematic splenic evaluation in nodal NHL for accurate staging and optimal therapeutic planning in our resource-constrained setting.

Keywords: Non-Hodgkin lymphoma, splenic involvement, histopathological patterns, nodular lymphoma, Pakistan, multicenter study.

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) comprises a biologically and clinically heterogeneous group of lymphoproliferative disorders originating from B-, T-, or natural killer (NK) cells, with marked variability in morphology, immunophenotype, genetic alterations, and clinical course. Globally, NHL constitutes a major proportion of hematological malignancies, with increasing incidence attributed to demographic transitions, environmental exposures, and improved

diagnostic capabilities [1,2]. Among the diverse subtypes, nodular (follicular-patterned) NHL represents a significant clinicopathological entity, particularly in adult populations, characterized by a relatively indolent course but a propensity for systemic dissemination, including extranodal organ involvement [3]. The spleen, as a central secondary lymphoid organ, plays a pivotal role in immune surveillance, antigen processing, and lymphocyte recirculation. Its unique microanatomical compartments white pulp, red pulp, and marginal zone provide a conducive microenvironment for lymphoid proliferation and infiltration [4]. Consequently, splenic involvement is a well-recognized feature in NHL and is incorporated into staging systems such as the Ann Arbor classification, where its presence frequently signifies advanced disease (stage III/IV) with important prognostic and therapeutic implications [5]. Accurate identification of splenic infiltration is therefore critical for disease stratification and management planning. Histopathologically, splenic involvement in NHL demonstrates distinct architectural patterns, including nodular, diffuse, mixed, and miliary infiltration. These patterns reflect underlying tumor biology and dissemination pathways and often correlate with specific lymphoma subtypes. For instance, follicular lymphoma typically exhibits a nodular or follicular growth pattern within the white pulp, whereas diffuse large B-cell lymphoma (DLBCL) is more commonly associated with diffuse effacement of splenic architecture [6,7]. Mantle cell lymphoma and marginal zone lymphoma may demonstrate mixed or marginal zone–predominant infiltration patterns, further emphasizing the diagnostic relevance of histomorphological evaluation [8]. Recognition of these patterns is essential not only for accurate histopathological diagnosis but also for prognostic assessment and therapeutic decision-making. Despite significant advancements in radiological imaging modalities including ultrasonography, computed tomography (CT), and positron emission tomography (PET) definitive assessment of splenic involvement relies on histopathological confirmation. Minimally invasive techniques such as ultrasound-guided fine-needle aspiration cytology (FNAC) and core needle biopsy, complemented by immunohistochemistry (IHC), enable precise subclassification of NHL in accordance with the World Health Organization criteria [9]. However, in low- and middle-income countries, diagnostic approaches are often constrained by limited access to advanced imaging and molecular diagnostics, necessitating reliance on cost-effective and pragmatic methodologies.

In Pakistan, particularly in metropolitan regions such as Lahore, the burden of NHL is considerable; however, there is a notable scarcity of multicenter, systematically conducted studies evaluating splenic involvement patterns. Existing literature is largely limited to single-center experiences with small sample sizes and lacks comprehensive correlation between histopathological patterns, immunophenotypic subtypes, and clinicopathological variables. Given the influence of regional genetic, environmental, and healthcare factors on disease presentation, the generation of context-specific data is imperative for optimizing diagnostic algorithms and therapeutic strategies. The present multicenter cross-sectional study was designed to comprehensively evaluate the frequency and histopathological patterns of splenic involvement in patients with nodular NHL across major tertiary care centers in Lahore. By integrating imaging findings with cytomorphological, histopathological, and immunohistochemical analyses, this study aims to elucidate the relationship between splenic infiltration patterns, lymphoma subtypes, and key clinical parameters, thereby contributing to improved diagnostic precision and evidence-based clinical management.

Objectives of the Study

The primary objective of this study is to determine the frequency of splenic involvement in patients with Histopathologically confirmed nodular non-Hodgkin's lymphoma presenting to tertiary care hospitals in Lahore.

Significance of the Study

This study provides critical insights into the histopathological spectrum of splenic involvement in nodular NHL within a resource-constrained healthcare setting. By generating multicenter data, it addresses a significant gap in the regional literature and enhances the external validity and generalizability of findings in the Pakistani population. From a diagnostic perspective, the study emphasizes the importance of correlating morphological patterns with immunophenotypic subtypes, thereby improving diagnostic accuracy and reducing the likelihood of misclassification. This is particularly relevant in settings where access to advanced molecular diagnostics is limited. Furthermore, the identification of specific patterns associated with aggressive or advanced disease may facilitate early risk stratification and guide therapeutic decision-making. Clinically, the findings underscore the necessity of systematic evaluation of the spleen in all patients with nodular NHL, especially given its prognostic significance in staging and disease progression. The study also highlights the utility of cost-effective diagnostic modalities, such as ultrasonography and FNAC, in conjunction with histopathological assessment, thereby supporting their integration into routine clinical practice in low-resource settings. Finally, this research establishes a foundation for future large-scale, prospective studies and may contribute to the development of standardized national guidelines for the diagnosis and management of NHL. It also opens avenues for

further investigation into molecular and genetic determinants of splenic involvement, ultimately advancing precision medicine approaches in hematological oncology.

METHODOLOGY

This multicenter cross-sectional analytical study was conducted over a period of two years, from October 2023 to October 2025, across three major tertiary care institutions in Lahore, namely Fatima Memorial Hospital, Chughtai Lab & Healthcare, and Sir Ganga Ram Hospital. These centers were selected due to their high patient influx, well-established diagnostic infrastructure, and availability of specialized histopathology and immunohistochemistry facilities. The study enrolled a total sample size of 87 patients diagnosed with nodular non-Hodgkin's lymphoma (NHL), using a non-probability consecutive sampling technique to ensure inclusion of all eligible cases presenting during the study period.

The study population comprised adult patients (≥18 years) of either gender with histopathologically confirmed nodular NHL based on lymph node or extranodal tissue biopsy. Patients were included only if they had undergone radiological evaluation of the spleen and had complete clinical, laboratory, and histopathological records available. Cases with Hodgkin lymphoma, non-nodular variants of NHL, prior history of chemotherapy or radiotherapy before splenic assessment, or coexisting conditions affecting splenic morphology (such as chronic liver disease or portal hypertension) were excluded to minimize confounding factors and ensure diagnostic specificity. Data were collected prospectively using a structured and pre-validated data collection proforma. Demographic characteristics, including age and gender, along with clinical parameters such as presence of B-symptoms (fever, night sweats, and weight loss), lymphadenopathy, and laboratory findings, were systematically recorded. Disease staging was performed according to standard Ann Arbor criteria, integrating clinical evaluation, imaging findings, and bone marrow examination results where indicated. Assessment of splenic involvement was performed initially through abdominal ultrasonography for all patients to evaluate splenic size, parenchymal echotexture, and the presence of focal or diffuse lesions. In cases where focal lesions were identified, ultrasound-guided fine-needle aspiration cytology (FNAC) was performed under strict aseptic conditions by experienced radiologists. Cytological smears were prepared and stained using conventional techniques, including Giemsa and Papanicolaou stains, to facilitate preliminary morphological evaluation. Where clinically feasible, core needle biopsy specimens were obtained to allow more detailed histopathological assessment. The diagnosis of splenic involvement was established based on a combination of radiological, cytological, and histopathological findings. Histopathological evaluation of all tissue specimens was carried out using standardized laboratory protocols. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks were sectioned at 3–5 µm thickness and stained with hematoxylin and eosin (H&E) for detailed morphological analysis.

The patterns of splenic involvement were classified into four distinct categories nodular, diffuse, mixed, and miliary based on established histomorphological criteria. Nodular patterns were defined by discrete lymphoid aggregates predominantly involving the white pulp, while diffuse patterns demonstrated complete architectural effacement by neoplastic lymphoid cells. Mixed patterns exhibited features of both nodular and diffuse infiltration, whereas miliary patterns were characterized by multiple small, scattered nodules throughout the splenic parenchyma. All histopathological slides were independently reviewed by at least two experienced histopathologists to ensure diagnostic accuracy and minimize interobserver variability. Immunophenotypic characterization was performed using a panel of monoclonal antibodies following standardized immunohistochemical (IHC) techniques. The antibody panel included key markers such as CD20, CD3, CD5, CD10, BCL-2, BCL-6, Cyclin D1, and Ki-67 to facilitate lineage determination and subclassification. Antigen retrieval was performed using heat-induced epitope retrieval methods, followed by incubation with primary and secondary antibodies and visualization using appropriate chromogenic substrates. Classification of NHL subtypes was carried out in accordance with the World Health Organization criteria, enabling categorization into major subtypes such as diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and marginal zone lymphoma. Quality assurance measures were strictly implemented throughout the study to ensure reliability and reproducibility of findings. Standard operating procedures (SOPs) were adhered to for specimen collection, processing, staining, and reporting. Internal quality controls were included in each IHC run, and periodic interdepartmental reviews were conducted to resolve any diagnostic discrepancies through consensus among senior pathologists.

Statistical analysis was performed using the SPSS latest version. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. The frequency of splenic involvement was calculated along with 95% confidence intervals. Inferential statistical tests, including chi-square or Fisher's exact test, were applied to assess associations between splenic involvement and categorical clinicopathological variables, while independent t-

tests or analysis of variance (ANOVA) were used for continuous variables where appropriate. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Institutional Review Boards of all participating centers prior to commencement. Written informed consent was obtained from all participants, and strict confidentiality of patient data was maintained by anonymizing all records. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, ensuring adherence to international standards for biomedical research involving human subjects.

RESULTS

Demographic and Clinical Characteristics of the Study Population

Table 1: Baseline Demographic and Clinical Profile of Patients (n = 87)

Variable	*Category*	*Frequency (n)*	*Percentage (%)*
Age (years)	Mean ± SD	52.4 ± 16.7	—
Gender	Male	58	66.7
	Female	29	33.3
B-symptoms	Present	41	47.1
	Absent	46	52.9
Disease Stage	Stage I–II	34	39.1
	Stage III–IV	53	60.9
Bone Marrow Involvement	Present	26	29.9
	Absent	61	70.1

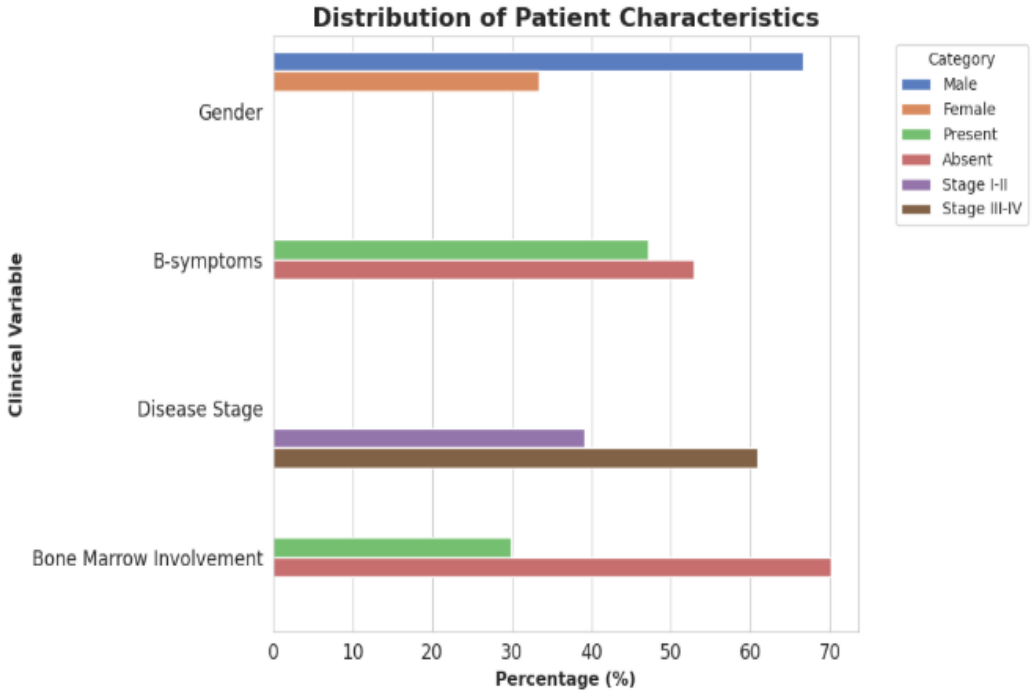

Fig 1: Baseline Demographic and Clinical Profile of Patients (n = 87)

A total of 87 patients with histopathologically confirmed nodular non-Hodgkin's lymphoma were included in the analysis. The mean age of the study population was 52.4 ± 16.7 years, indicating a predominance of middle-aged to elderly individuals. A marked male predominance was observed, with males comprising 66.7% of cases, yielding a male-to-female ratio of approximately 2:1.

Clinically, B-symptoms were present in nearly half of the patients (47.1%), reflecting a substantial proportion of patients presenting with systemic disease manifestations. In terms of disease staging, a majority (60.9%) were diagnosed at advanced stages (III–IV), highlighting delayed presentation or aggressive disease biology in the studied population. Additionally, bone marrow infiltration was identified in 29.9% of cases, suggesting a considerable burden of disseminated disease at diagnosis.

Frequency of Splenic Involvement

Table 2: Frequency of Splenic Involvement in Nodular NHL

Splenic Involvement	*Frequency (n)*	*Percentage (%)*	*95% CI*
Present	28	32.2	22.9–42.8
Absent	59	67.8	—

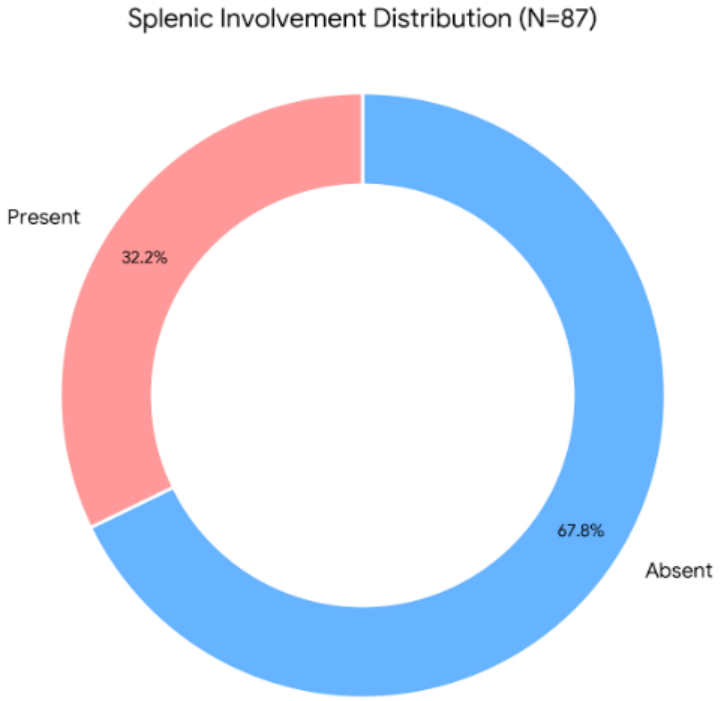

Fig 2: Frequency of Splenic Involvement in Nodular NHL

Splenic involvement was detected in 28 out of 87 patients, corresponding to a frequency of 32.2% (95% CI: 22.9–42.8). This indicates that approximately one-third of patients with nodular NHL exhibit splenic infiltration at the time of evaluation. The relatively high prevalence underscores the clinical importance of systematic splenic assessment during staging workup, particularly in resource-limited settings where underdiagnosis may occur.

Histopathological Patterns of Splenic Involvement

Table 3: Distribution of Histopathological Patterns in Splenic Involvement (n = 28)

Pattern	*Frequency (n)*	*Percentage (%)*
Nodular	13	46.4
Diffuse	9	32.1
Mixed	4	14.3
Miliary	2	7.1

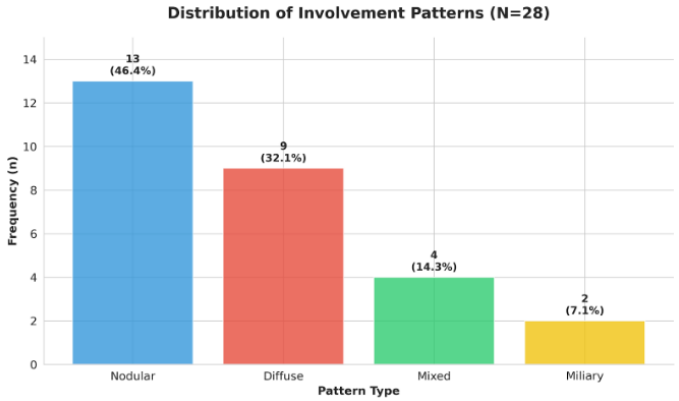

Fig 3: Distribution of Histopathological Patterns in Splenic Involvement

Among patients with confirmed splenic involvement, the nodular pattern was the most prevalent (46.4%), followed by the diffuse pattern (32.1%). Less frequently observed patterns included mixed (14.3%) and miliary (7.1%) infiltration. The predominance of the nodular pattern suggests preferential involvement of the splenic white pulp, particularly in indolent lymphoma subtypes. Conversely, the diffuse pattern reflects extensive architectural effacement, typically associated with more aggressive disease behavior. The relatively lower frequency of miliary involvement indicates that this pattern represents a less common mode of splenic dissemination in nodular NHL.

Distribution of NHL Subtypes

Table 4: Immunohistochemical Subtypes of Nodular NHL (n = 87)

NHL Subtype	*Frequency (n)*	*Percentage (%)*
Diffuse Large B-cell Lymphoma (DLBCL)	45	51.7
Follicular Lymphoma	22	25.3
Mantle Cell Lymphoma	11	12.6
Marginal Zone Lymphoma	7	8.0
Others	2	2.3

Diffuse large B-cell lymphoma (DLBCL) emerged as the most common subtype (51.7%), followed by follicular lymphoma (25.3%), mantle cell lymphoma (12.6%), and marginal zone lymphoma (8.0%). This distribution reflects the predominance of aggressive B-cell lymphomas in the studied population. However, the significant proportion of follicular lymphoma indicates the coexistence of indolent variants, which may exhibit distinct patterns of splenic involvement. The subtype distribution is consistent with global epidemiological trends, though slight regional variations may exist.

Association Between Splenic Involvement and Clinicopathological Variables

Table 5: Association of Splenic Involvement with Clinical Parameters

Variable	*Splenic Involvement Present (%)*	*p-value*
Advanced Stage (III–IV)	78.6	<0.001
B-symptoms	64.3	0.008
Bone Marrow Involvement	53.6	0.02

Statistical analysis demonstrated a highly significant association between splenic involvement and advanced disease stage ($p < 0.001$), with the majority of affected patients presenting in stages III–IV. And splenic involvement was significantly correlated with the presence of B-symptoms ($p = 0.008$), suggesting that systemic inflammatory or tumor burden markers are closely linked with splenic infiltration. A significant association was also observed with bone marrow involvement ($p = 0.02$), indicating that splenic infiltration frequently coexists with other forms of extranodal dissemination. Collectively, these findings reinforce the role of splenic involvement as a marker of advanced and systemic disease progression.

Correlation Between Histopathological Patterns and NHL Subtypes

Table 6: Pattern Distribution According to NHL Subtype (n = 28)

Subtype	*Nodular (%)*	*Diffuse (%)*	*Mixed (%)*	*Miliary (%)*
DLBCL	22.2	55.6	16.7	5.5
Follicular Lymphoma	69.2	15.4	15.4	0
Mantle Cell Lymphoma	36.4	36.4	18.2	9.0
Marginal Zone Lymphoma	42.9	28.6	14.3	14.3

A distinct correlation was observed between histopathological patterns of splenic involvement and NHL subtypes. The nodular pattern was predominantly associated with follicular lymphoma (69.2%), reflecting its characteristic follicular growth pattern. The diffuse pattern was most frequently observed in DLBCL (55.6%), consistent with its aggressive biological behavior and tendency to efface normal splenic architecture. Mantle cell lymphoma exhibited a relatively heterogeneous distribution, with both nodular and diffuse patterns observed equally (36.4% each), indicating intermediate biological behavior. Marginal zone lymphoma demonstrated variable patterns, though nodular involvement remained relatively common. These findings highlight the diagnostic value of histomorphological assessment in predicting underlying lymphoma subtype.

DISCUSSION

The present multicenter study provides comprehensive insight into the frequency and histopathological spectrum of splenic involvement in nodular non-Hodgkin's lymphoma (NHL) within a Pakistani population. The findings demonstrate that splenic infiltration occurs in approximately one-third of patients, with distinct morphological patterns correlating strongly with lymphoma subtype and disease stage. These observations are consistent with contemporary literature and reinforce the biological and clinical significance of splenic involvement in NHL. Splenic involvement in NHL is widely recognized as a manifestation of systemic disease dissemination rather than a primary process in the majority of cases. Previous studies have reported that approximately 30–40% of NHL patients develop splenic infiltration during the course of the disease, which is comparable to the frequency observed in the present study (32.2%) [10]. This similarity suggests that the burden of splenic involvement in the studied population aligns with global trends, despite regional differences in healthcare access and diagnostic infrastructure. The relatively high frequency observed may also be attributed to the use of combined imaging and cytological assessment, which enhances diagnostic sensitivity compared to imaging alone. The demographic profile observed in this study, including a mean age in the fifth decade and male predominance, is in agreement with previously reported epidemiological data on NHL. Studies conducted in developing countries, including Pakistan, have consistently demonstrated a higher incidence among males and a tendency toward presentation at relatively younger ages compared to Western populations [11]. This may reflect underlying genetic susceptibility, environmental exposures, or delayed healthcare-seeking behavior. A key finding of the present study is the predominance of the nodular pattern of splenic involvement, followed by diffuse infiltration. This observation is supported by classical histopathological studies, which describe nodular (white pulp–based) infiltration as the initial and most common pattern in low-grade lymphomas, with progression to diffuse red pulp involvement in advanced disease stages [12]. Ultrasonographic and pathological correlation studies have similarly demonstrated that nodular lesions account for the majority of splenic involvement, whereas diffuse infiltration represents a secondary or advanced pattern [13]. The relatively lower frequency of miliary and mixed patterns in this study further supports their classification as less common morphological variants. The association between histopathological patterns and lymphoma subtypes observed in this study is particularly noteworthy. The nodular pattern predominated in follicular lymphoma, which is consistent with its origin from germinal center B cells and its characteristic follicular architecture. In contrast, diffuse large B-cell lymphoma (DLBCL) showed a predominance of diffuse infiltration, reflecting its aggressive nature and tendency to cause architectural effacement. Similar findings have been reported in earlier studies, where DLBCL demonstrated macronodular or diffuse splenic involvement, often associated with rapid disease progression [14]. Mantle cell lymphoma and marginal zone lymphoma exhibited more heterogeneous patterns, which is in line with their intermediate biological behavior and variable growth patterns. Another significant finding of this study is the strong association between splenic involvement and advanced-stage disease (stage III/IV). This is consistent with established staging systems such as the Ann Arbor classification, where splenic infiltration is considered a marker of disseminated disease [10]. The observed correlation with B-symptoms further

supports the role of splenic involvement as an indicator of systemic inflammatory response and high tumor burden. Similar associations have been reported in previous studies, where patients with splenic infiltration were more likely to present with constitutional symptoms and aggressive disease phenotypes. The relationship between splenic involvement and bone marrow infiltration observed in this study is also well supported in the literature. Both spleen and bone marrow represent key components of the reticuloendothelial system, and their simultaneous involvement reflects widespread hematogenous dissemination of malignant lymphoid cells. Studies have demonstrated that bone marrow infiltration occurs in approximately 30% of NHL cases, closely paralleling the findings of the present study [15]. The coexistence of splenic and bone marrow involvement therefore has important implications for disease staging, prognosis, and therapeutic planning. From a pathological perspective, the findings of this study highlight the importance of integrating morphological and immunophenotypic evaluation for accurate diagnosis. The WHO classification emphasizes the role of immunohistochemistry in distinguishing between various NHL subtypes, particularly in extranodal sites such as the sple, where morphological overlap may occur [11]. The use of a comprehensive IHC panel in this study allowed precise subclassification, thereby enhancing diagnostic accuracy and clinical relevance. The predominance of DLBCL as the most common subtype in this cohort is consistent with global data, where it accounts for approximately 40–50% of NHL cases. Similar distributions have been reported in studies evaluating extranodal lymphoma involvement, including hepatic and splenic sites, further validating the findings of this study [16]. However, the relatively high proportion of follicular lymphoma underscores the importance of recognizing indolent subtypes that may exhibit distinct patterns of splenic infiltration and clinical behavior.

Limitations Of The Study

Despite the strengths of the present multicenter investigation, several limitations should be acknowledged when interpreting the findings. Firstly, the study employed a cross-sectional design, which inherently limits the ability to establish temporal relationships or causal inferences between splenic involvement and disease progression. While associations with advanced stage, B-symptoms, and bone marrow infiltration were identified, longitudinal follow-up would be required to determine the prognostic impact of specific histopathological patterns on survival outcomes and treatment response. Secondly, the sample size (n = 87), although adequate for preliminary statistical analysis, remains relatively modest, particularly when stratified into multiple lymphoma subtypes and splenic involvement patterns. This may reduce the statistical power to detect subtle associations and limits the generalizability of subgroup analyses. Additionally, the study population was restricted to tertiary care centers within Lahore, which may introduce selection bias, as these centers often receive more advanced or referred cases, potentially overestimating the frequency of splenic involvement and advanced-stage disease. Another important limitation relates to the diagnostic methodology for splenic assessment. Although ultrasonography combined with fine-needle aspiration cytology (FNAC) and histopathological evaluation provides a pragmatic and cost-effective approach, it may have lower sensitivity compared to advanced imaging modalities such as PET-CT. Small or diffuse infiltrative lesions, particularly in early disease, may have been underdiagnosed. Furthermore, not all cases underwent core biopsy, which could limit comprehensive architectural assessment in certain instances.

Future Perspectives

Future research should focus on large-scale, multicenter prospective studies encompassing diverse geographic regions of Pakistan and beyond to enhance the external validity and generalizability of findings. A longitudinal design would allow for the evaluation of prognostic implications of splenic involvement, including its impact on overall survival, progression-free survival, and response to therapy across different NHL subtypes. The integration of advanced imaging modalities, particularly positron emission tomography–computed tomography (PET-CT), should be prioritized to improve the sensitivity and specificity of splenic involvement detection. Comparative studies evaluating ultrasonography, CT, and PET-CT in resource-limited versus resource-rich settings would provide valuable insights into optimizing diagnostic algorithms based on cost-effectiveness and accessibility. Incorporation of molecular and genomic profiling represents a critical future direction. The application of next-generation sequencing (NGS) and gene expression profiling could elucidate the molecular pathways underlying different patterns of splenic infiltration and facilitate the identification of novel biomarkers for early detection and risk stratification. Such approaches would also support the transition toward precision medicine in lymphoma management.

CONCLUSION

This study provides important multicenter evidence highlighting that splenic involvement is a relatively common finding in nodular non-Hodgkin's lymphoma, occurring in approximately one-third of patients in the studied population. The analysis demonstrates that nodular and diffuse patterns are the predominant histopathological forms, each exhibiting a distinct association with specific lymphoma subtypes. Notably, the nodular pattern was primarily linked with follicular lymphoma, whereas diffuse

infiltration was more frequently observed in diffuse large B-cell lymphoma, reflecting underlying differences in tumor biology. The study further establishes a significant association between splenic involvement and advanced-stage disease, presence of B-symptoms, and bone marrow infiltration, underscoring its role as an indicator of systemic disease burden and progression. These findings reinforce the importance of incorporating systematic splenic evaluation into routine staging protocols, particularly in patients presenting with high-risk clinical features. From a diagnostic standpoint, the study demonstrates that a combined approach utilizing ultrasonography, cytology, histopathology, and immunohistochemistry can provide reliable and clinically meaningful assessment of splenic involvement, even in resource-constrained settings. This has important implications for improving diagnostic workflows and optimizing patient management in developing healthcare systems. The findings emphasize that histopathological characterization of splenic involvement is not merely descriptive but carries significant diagnostic, prognostic, and therapeutic relevance. The integration of morphological patterns with immunophenotypic and clinical data can enhance disease stratification and support evidence-based clinical decision-making. Future advancements incorporating molecular diagnostics and advanced imaging are expected to further refine the understanding and management of splenic involvement in non-Hodgkin's lymphoma.

Conflict of interest

The authors declared no conflict of interest.

Author Contribution

Concept & Design of the study: Madiha Iqbal & Atif Munir

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Data analysis: Hamid Nawaz Khokhar

Critical Review & Final approval: Muhamamad Ali Zahid & Madiha Iqbal

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the study's integrity.

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